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# Health and Environmental Effects Profile for Selected Toluenediamines

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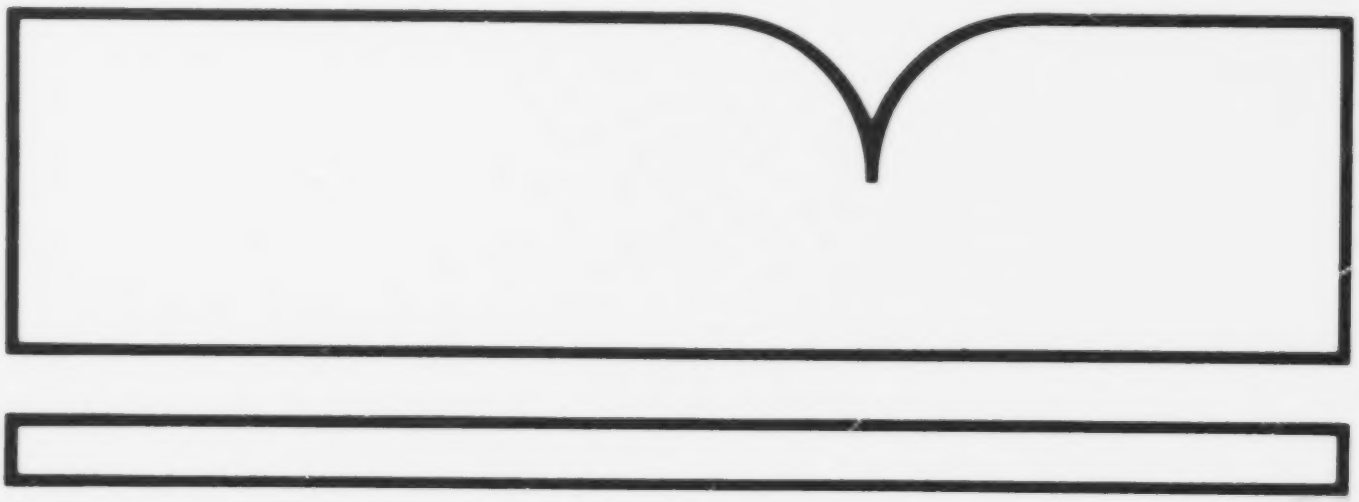

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# HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR SELECTED TOLUENEDIAMINES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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16. ABSTRACT

The Health and Environmental Effects Profile for Selected Toluene Diamines was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. 2,5-Toluene diamine and 2,6-Toluene diamine have been determined to be systemic toxicants. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for 2,5-Toluene diamine is $5.6 \times 10^{-1}$ (mg/kg bw/day) and for 2,6-Toluene diamine is $1.6 \times 10^{-1}$ (mg/kg bw/day) for oral exposure.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for other Selected Toluene Diamine isomers.


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## PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or $q_1^*$ is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

## ACKNOWLEDGEMENTS

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# 1. INTRODUCTION

## 1.1. STRUCTURE AND CAS NUMBER

Toluenediamine is the commercial mixture composed of six isomers, 2,4-toluenediamine, 2,6-toluenediamine, 2,3-toluenediamine, 3,4-toluenediamine, 2,5-toluenediamine and 3,5-toluenediamine (Milligan and Gilbert, 1978). This hazard profile will address only the commercial mixture and the four isomers: 2,5-toluenediamine, 3,4-toluenediamine, 2,6-toluenediamine and 2,3-toluenediamine.

The molecular formula for toluenediamine and its isomers is $C_7H_{10}N_2$ and the molecular weight of these compounds is 122.2. Toluenediamine (commercial mixture) is also known as diaminotoluene and methylphenylene diamine (NIOSH, 1978). The Chemical Abstract Service (CAS) Registry Number is 25376-45-8. The structure, CAS numbers and common synonyms for the 4 isomers addressed in this profile are included in Table 1-1.

Toluene-2,5-diamine sulfate (CAS No. 6369-59-1) is a salt of toluene-2,5-diamine and sulfuric acid and is used in place of toluene-2,5-diamine in many of the studies cited in this profile. Both compounds are used in hair-dye formulations (IARC, 1978).

## 1.2. PHYSICAL AND CHEMICAL PROPERTIES

Some of the physical properties of toluenediamine and the 4 isomers are listed in Table 1-2.

## 1.3. PRODUCTION DATA

The toluenediamines are prepared by the dinitration of toluene, which occurs in two stages. Mononitration occurs in a mixed acid of 30% $HNO_3$ and 55% $H_2SO_4$ at 30-70°C. The mononitrotoluenes formed are then nitrated with 30% $HNO_3$ and 63% $H_2SO_4$ to yield 78% 2,4-, 19.5% 2,6-,

TABLE 1-1

Structure, CAS Numbers and Common Synonyms for 2,5-TDA, 3,4-TDA, 2,6-TDA and 2,3-TDA

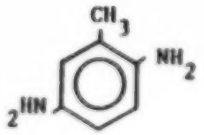
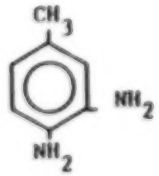
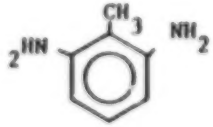
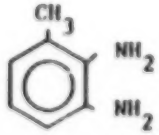
| Compound | Structure | CAS Number | Common Synonyms |
|---|---|---|---|
| Toluene-2,5-diamine |  | 95-70-5 | 2-methyl-1,4-benzene-diamine; 4-amino-2-methyl aniline; 2-methyl-para-phenylene diamine; para-toluenediamine and para, metatolylene diamine (IARC, 1978). |
| Toluene-3,4-diamine |  | 496-72-0 | 4-methyl-1,2-benzenediamine; 3,4-diaminotoluene and 3,4-toluylenediamine (NIOSH, 1978) |
| Toluene-2,6-diamine |  | 823-40-5 | 2-methyl-1,3-benzene-diamine; 2,6-diaminotoluene and 2,6-toluylene diamine (NIOSH, 1978) |
| Toluene-2,3-diamine |  | 2687-25-4 | 3-methyl-1,2-benzene-diamine; 1,2-diamino-3-methylbenzene and 2,3-toluylenediamine (U.S. EPA/NIH, 1983) |

TABLE 1-2

Physical Properties of Toluenediamine
(Commercial Mixture) and the Four Isomers

| Isomer | 2,3- | 2,5- | 2,6- | 3,4- | Commercial Mixture |
|---|---|---|---|---|---|
| Melting point °C:[a] | 63-64 | 99 | 105 | 88.5 | 90 |
| Boiling point °C:[a] | 255 | 292 | NR | 265 | 283 |
| Vapor pressure (mm Hg)[a] | | | | | |
| at 150°C: | 0.009 | NR | 0.016 | NR | NR |
| at 160°C: | 0.014 | NR | 0.025 | NR | NR |
| at 180°C: | 0.02 | NR | 0.057 | NR | NR |
| Solubility:[a] | NR | soluble in water | NR | NR | NR |
| Log octanol/water partition coefficients:[b] | 0.65 | 0.25 | 0.5 | 0.65 | 1.96[c] |

[a]Source: Milligan and Gilbert, 1978

[b]Source: Federal Register, 1982

[c]1.96 is the log bioconcentration factor determined experimentally by Mackay, 1982

NR = Not reported

0.7% 2,5-, 1.5% 2,3- and 2.5% 3,4-dinitrotoluene (Milligan and Gilbert, 1978). These dinitrotoluenes are subsequently catalytically hydrogenated to the corresponding toluenediamines.

The commercial mixture of toluenediamines and the four isomers are produced by a number of manufacturers (Table 1-3). The principal areas of production for all the compounds are Louisiana, West Virginia, New Jersey, Texas, Kentucky and New York (U.S. EPA, 1983).

Practically all the toluenediamine produced is captively consumed in the production of toluene diisocyanate (SRI, 1976). In 1982, 695 million pounds of toluene diisocyanate were produced (SRI, 1983). Some toluenediamine (unknown amount) is used in manufacturing polymers and dyes for hair, fabrics and fur (Thirtle, 1968).

TABLE 1-3

Producers of Toluenediamine and Four of the Isomers*

| Isomer | Manufacturer | Location | Production Volume (lbs) |
|---|---|---|---|
| Toluenediamine (commercial mixture) | Mobay Chemical Co. | Marshall, WV | NR |
| | | Chambers, TX | NR |
| | Union Carbide Corp. | Kanawha, WV | NR |
| | BASF Wyandotte Corp. | Geismar, LA | 50,000,000-100,000,000 |
| | Allied Chemical Co. | Moundsville, WV | 50,000,000-100,000,000 |
| | Rubicon Chemicals, Inc. | Geismar, LA | NR |
| Toluene-2,5-diamine | Air Products and Chemicals, Inc. | Pasadena, TX | 100,000-1,000,000 |
| Toluene-3,4-diamine | Kodak Park Division | Rochester, NY | 10,000-100,000 |
| | Olin Corp. | Brandenburg, KY | 100,000-1,000,000 |
| | BASF Wyandotte Corp. | Geismar, LA | 100,000-1,000,000 |
| | Allied Chemical Co. | Moundsville, WV | NR |
| | Air Products and Chemicals, Inc. | Pasadena, TX | 100,000-1,000,000 |
| | DuPont and Co. | Deepwater, NJ | 100,000-1,000,000 |
| Toluene-2,6-diamine | Olin Corp. | Lake Charles, LA | 10,000,000-50,000,000 |
| | | Brandenburg, KY | 1,000,000-10,000,000 |
| | Union Carbide Corp. | Kanawha, WV | NR |
| | BASF Wyandotte Corp. | Geismar, LA | 10,000,000-50,000,000 |
| | Allied Chemical Corp. | Moundsville, WV | NR |
| Toluene-2,3-diamine | Olin Corp. | Brandenburg, KY | 100,000-1,000,000 |
| | BASF Wyandotte Corp. | Geismar, LA | 1,000,000-10,000,000 |
| | Allied Chemical Co. | Moundsville, WV | NR |
| | Air Products and Chemicals, Inc. | Pasadena, TX | 1,000,000-10,000,000 |
| | DuPont and Co. | Deepwater, NJ | 100,000-1,000,000 |

*Source: U.S. EPA, 1983
NR = Not reported

## 2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Data regarding the fate and transport of the toluenediamines in the environment are sparse. Although no data were available on the persistence of these compounds, it is expected that they may undergo rapid transformation in the environment since the aromatic amines are relatively reactive compounds.

The log octanol-water partition coefficient for each of the 4 isomers is <0.65 (see Table 1-2) and the log BCF for the commercial mixture is 1.96 (Mackay, 1982). These data suggest that there is little potential for bioaccumulation in aquatic organisms. Because the alkaline nature of these compounds, it is likely that they will react with acids in the aqueous or soil media to form salts. Although no specific data were available, the fate and transport of the compounds in these environments may then depend on their ability to dissolve in water or leach through soil columns. Additional data regarding the fate and transport of the toluenediamines in the soil, water or atmospheric environments were not located in the available literature.

## 3. EXPOSURE

Toluenediamines are used either directly in hair dyes as color-yielding compounds or as chemical intermediates in the synthesis of diisocyanates or dyes; therefore, exposure to these compounds will be greatest in the manufacturing facilities or from consumer use of products containing these dyes. According to the Federal Register (1982) the U.S. EPA reported that ~15 million people are potentially exposed to the toluenediamines and other phenyldiamines as a result of personal use or in the application of hair dyes to other people (47 FR 979). Exposure may also result from the manufacture or use of products containing these chemicals. Toluenediamine concentrations of 0.006-0.39 mg/m$^3$ were measured in the work air of an Olin Chemical Company manufacturing facility (Ahrenholz, 1980). Toluene-2,6-diamine (an intermediate in the production of toluenediisocyanate) was detected in aqueous extracts from food-packaging products (boil-in-bags and retortable pouches) at levels ranging from <0.1-2.2 ppb (Snyder et al., 1982).

## 4. PHARMACOKINETICS

### 4.1. ABSORPTION

A 1.6% aqueous solution of [methyl-$^{14}$C]-labeled toluene-2,5-diamine hydrochloride (10 mg toluene-2,5-diamine) was administered by gavage to male and female rats. Within 24 hours, >70% of the administered radioactivity was excreted in the urine and <5% was excreted in the feces (Hruby, 1977). These data suggest that toluene-2,5-diamine is efficiently absorbed from the gastrointestinal tract of rats following oral administration.

Hruby (1977) applied dermally 7.5 mg $^{14}$C-toluene-2,5-diamine (pH 10.1) to rats and 1.4 g $^{14}$C-toluene-2,5-diamine (pH 10.1) to dogs. The position of the label was as noted above for the oral experiments. Approximately 0.2% of the administered radioactivity was absorbed through the skin of rats and 0.127% was cutaneously absorbed in the dog as indicated by the amount excreted in the urine and feces plus the amount in the total-body homogenate (Hruby, 1977).

About 40 mg of toluene-2,5-diamine was absorbed through the skin of dogs during application of toluene-2,5-diamine sulfate (1.4 g toluene-2,5-diamine) in 50 mℓ of a lauryl sulfate-based gel (pH 9.5) to the hair and skin for 3 hours. The amount of toluene-2,5-diamine absorbed decreased to <3 mg when 3% hydrogen peroxide was present in the gel, simulating hair-dyeing conditions (Kiese et al., 1968). Urinary excretion data were used to estimate absorption.

Kiese and Rauscher (1968) found that application of a hair dyeing preparation containing 2.5 g of toluene-2,5-diamine sulfate and 2.5 g resorcinol with 3% hydrogen peroxide (pH 9.5) to the hair and scalp of human subjects for 40 minutes resulted in the absorption of ~4.6 mg toluene-2,5-diamine. This value was calculated from urinary excretion data.

## 4.2. DISTRIBUTION

Hruby (1977) administered by gavage a 1.6% aqueous solution of [methyl-$^{14}$C]-labeled toluene-2,5-diamine hydrochloride containing 10 mg of toluene-2,5-diamine to rats and found 1.4 $\pm$ 0.02% of the radioactivity in the gastrointestinal tract and 1.2 $\pm$ 0.08% in the total-body homogenate after 5 days. Following cutaneous application of 7.5 mg $^{14}$C-toluene-2,5-diamine (pH 10.1) to rats, ~0.1% of the radioactivity was found in the total-body homogenate and ~7.2% remained at the site of application (Hruby, 1977).

## 4.3. METABOLISM

Following dermal application of 2.5 g of toluene-2,5-diamine sulfate and 2.5 g resorcinol with hydrogen peroxide (pH 9.5) to humans, ~3.7 mg N,N'-diacetyl-p-toluenediamine appeared in the urine. Following subcutaneous injection of 5.5 mg toluene-2,5-diamine, 47.6% of the dose was excreted as N,N'-diacetyl-p-toluenediamine (~4.5 mg) in the urine of humans (Kiese and Rauscher, 1968).

## 4.4. EXCRETION

Excretion of toluene-2,5-diamine (or metabolites) in the urine of dogs and rats appears to occur more rapidly and extensively following oral, subcutaneous or intravenous administration than following cutaneous application of the compound. Excretion of the metabolite N,N'-diacetyl-p-toluenediamine in humans occurs slowly whether toluene-2,5-diamine is applied dermally or injected subcutaneously.

Following administration by gavage of a 1.6% aqueous solution of $^{14}$C-toluene-2,5-diamine hydrochloride (10 mg toluene-2,5-diamine) to rats, >70% of the radioactivity was excreted in the urine and <5% was excreted in the feces within 24 hours. Excretion of the radioactivity in the urine and feces was essentially complete within 5 days (Hruby, 1977).

Cutaneous application of 7.5 mg $^{14}$C-toluene-2,5-diamine (pH 10.1) to rats resulted in 0.08-0.14% of the radioactivity being excreted in the urine and 0.004% excreted in the feces within 24 hours (Hruby, 1977). Following dermal application of 1.4 g $^{14}$C-toluene-2,5-diamine (pH 10.1) to dogs, the amount of radioactivity excreted in the urine and feces over 4 days totalled 0.092±0.009% and 0.840±0.10%, respectively, of the administered dose (Hruby, 1977).

Approximately 0.41 mg of toluene-2,5-diamine was excreted in the urine within 24 hours after application of 1.4 g toluene-2,5-diamine (as the sulfate; pH 9.5) to the skin of dogs. The urine collected on the second day contained nearly 0.1 mg and traces of toluene-2,5-diamine were detected in the urine on the third day (Kiese et al., 1968).

Following application of hair-dye preparations containing 2.5 g toluene-2,5-diamine sulfate and 2.5 g resorcinol with 3% hydrogen peroxide (pH 9.5) to humans, 3661 µg of N,N'-diacetyl-p-toluenediamine was excreted in the urine within 48 hours (Kiese and Rauscher, 1968).

Following intravenous administration of 0.14 g [methyl-$^{14}$C]-labeled toluene-2,5-diamine to dogs, total amounts of radioactivity excreted in the urine and feces were 60±8.0% and 19±4.0% of the administered dose, respectively. The majority of the 4-day excretion occurred within the first 24 hours (Hruby, 1977).

Subcutaneous injection of a 0.4% aqueous solution of $^{14}$C-toluene-2,5-diamine (containing 3-5 mg of toluene-2,5-diamine and labeled in the position described above) resulted in ~67% of the radioactivity being excreted in the urine and <5% being excreted in the feces of rats within 24 hours (Hruby, 1977).

Following the subcutaneous injection of 5.54 mg toluene-2,5-diamine (as the sulfate) in aqueous solution to humans, 4455 µg of N,N'-diacetyl-p-toluene-diamine (47.6%) was excreted in the urine within 48 hours (Kiese and Rauscher, 1968).

## 5. EFFECTS

### 5.1. CARCINOGENICITY

A dietary carcinogenicity bioassay of toluene-2,5-diamine sulfate was conducted by the National Cancer Institute (NCI, 1978) using Fischer 344 rats and B6C3F1 mice. Fifty animals of each sex and species were maintained on diets containing TWA concentrations of 0, 0.06 or 0.2% for rats and 0, 0.06 or 0.10% toluene-2,5-diamine sulfate for mice for 78 weeks. No statistically significant change in the incidences of tumors were observed in either male or female mice or rats under the conditions of this bioassay (NCI, 1978).

Sufficient evidence was not obtained to demonstrate the carcinogenicity of toluene-2,6-diamine dihydrochloride in rats and mice (NCI, 1980). Groups of 50 rats of each sex were fed diets containing 0, 50, 250 or 500 ppm toluene-2,6-diamine dihydrochloride for 103 weeks and observed for an additional week. Similarly, 50 mice of each sex were fed 0, 50 or 100 ppm toluene-2,6-diamine dihydrochloride for 103 weeks (NCI, 1978). A statistically significant increase in interstitial-cell neoplasms of the testes was observed in rats, but this was not considered treatment-related since these neoplasms are common in rats and have a highly variable incidence. Conclusive evidence of a carcinogenic effect of toluene-2,6-diamine hydrochloride for mice or rats was not provided under the conditions of this bioassay.

Fifty male and 50 female Swiss Webster mice received weekly or fortnightly dermal applications for 18 months of 0.05 mL hair-dye preparations (1 volume of 3% toluene-2,5-diamine sulfate and 1.5% p-phenyldiamine with either 0.2% toluene-2,4-diamine, 0.38% 2,4-diaminoanisole sulfate or 0.17% M-phenylene-diamine mixed with an equal volume of 6% hydrogen peroxide) (Burnett et al., 1975). No statistically significant increase in the

incidences of lung tumors was observed in the test animals when compared with the controls. Limited data were available from a similar study in which 28 male and 28 female Swiss Webster mice were dermally treated once weekly for an unspecified period of time with 0.05 mℓ of a hair-dye formulation (1 volume of 3% toluene-2,5-diamine sulfate, 1.5% p-phenylenediamine and either 0.2 or 0.6% toluene-2,4-diamine mixed with an equal volume of 6% hydrogen peroxide) (Giles et al., 1976). Data from this study were deemed inadequate for the evaluation of the carcinogenicity of toluene-2,5-diamine sulfate (IARC, 1978).

Kinkel and Holzman (1973) tested three hair-dye preparations (1 volume of 0, 3 or 4% toluene-2,5-diamine mixed with an equal volume of 6% hydrogen peroxide). Fifty male and 50 female Sprague-Dawley rats were dermally treated twice weekly with 0.5 mℓ for 2 years. No statistically significant differences were observed in tumor incidences between the experimental and control group.

## 5.2. MUTAGENICITY

Many mutagenicity bioassays of toluene-2,5-diamine, toluene-2,6-diamine and toluene-3,4-diamine have been conducted using a variety of test systems. These studies are summarized in Tables 5-1, 5-2 and 5-3.

Toluene-2,5-diamine gave positive results in the Salmonella typhimurium (strain TA1538) reverse mutation assay, but only when assayed with a mammalian metabolic activation system (rat liver S-9) (Ames et al., 1975). This compound was also positive in the transformation assay with primary and secondary hamster embryo cells (HEC), before and after the addition of Simian Adenovirus (SA7) (Greene and Friedman, 1980). Toluene-2,5-diamine sulfate was inactive in the in vivo micronucleus test with rats (Hossack and Richardson, 1977), but exhibited a positive, dose-related response in the in vivo testicular DNA synthesis bioassay with mice (Greene et al., 1981).

TABLE 5-1

Mutagenicity Testing for Toluene-2,5-Diamine

| Assay | Indicator Organism | Application | Concentration or Dose | Activation System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium TA1538 | spot test | 0.25 mg/mℓ or 10 mg/mℓ | ±S9 | ± | Addition of $H_2O_2$ resulted in a 40-fold increase in revertants when S9 was present. | Ames et al., 1975 |
| Transformation assay | Syrian Golden primary HEC | plate incorporation | 3.13-50.0 µg/mℓ | NR | + | Before addition of SA7 | Greene and Friedman, 1980 |
| Transformation assay | Syrian Golden primary HEC | plate incorporation | 1.0-5.0 µg/mℓ | NR | + | After addition of SA7 | Greene and Friedman, 1980 |
| Transformation assay | Syrian Golden secondary HEC | plate incorporation | 1.0-50.0 µg/mℓ | NR | + | Chemical transformation of HEC | Greene and Friedman, 1980 |
| Micronucleus test | CFY rats (5 males/ 5 females) | by gavage | total dose: 120 mg/kg in 0.5% gum tragacanth with 0.5% sodium sulfite | NA | - | NC | Hossack and Richardson, 1977 |
| Testicular DNA synthesis | C57Bl/6 x C3H mice | intraperitoneally | 40.0-55.0 mg/kg | NA | + | Dose related at ≥40 mg/kg; significantly inhibited the incorporation of [$^{125}$I]iododeoxyuridine into murine testicular DNA | Greene et al., 1981 |

NR - Not reported
NC - No comment
NA - Not applicable

TABLE 5-2

Mutagenicity Testing for Toluene-2,6-Diamine

| Assay | Indicator Organism | Application | Concentration or Dose | Activation System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium TA98<br>TA100<br>TA1535<br>TA1537 | plate incorporation | 0.03-30 µmoles/plate | ±S9<br>±S9<br>±S9<br>±S9 | ±<br>±<br>-<br>- | Dose-related ≥0.03 µmoles/plate for TA98 and TA100 | Florin et al., 1980 |
| Transformation assay | Syrian Golden primary HEC | plate incorporation | 313.0-5000.0 µg/mL | NR | + | Marginally active before addition of SA7 | Greene and Friedman, 1980 |
| Transformation assay | Syrian Golden primary HEC | plate incorporation | 150.0-750.0 µg/mL | NR | + | After addition of SA7 | Greene and Friedman, 1980 |
| Transformation assay | Syrian Golden secondary HEC | plate incorporation | 0.5-200.0 µg/mL | NR | + | Chemical transformation | Greene and Friedman, 1980 |
| DNA repair assay | Fischer 344 male rats | by gavage in corn oil | 5.0 and 20.0 mg/kg | NA | - | NC | Mirsalis et al., 1982 |
| Testicular DNA synthesis | C57B1/6 x C3H mice | intraperitoneally | 30.0-100.0 mg/kg | NA | - | NC | Greene et al., 1981 |

NR = Not reported
NC = No comment
NA = Not applicable

TABLE 5-3

Mutagenicity Testing for Toluene-3,4-Diamine

| Assay | Indicator Organism | Application | Concentration or Dose | Activation System | Response | Comment | Reference |
|---|---|---|---|---|---|---|---|
| Reverse mutation | Salmonella typhimurium | spot test | 3 μmoles/plate | | | NC | Florin et al., 1980 |
| | TA98 | | | ±S9 | - | | |
| | TA100 | | | ±S9 | - | | |
| | TA1535 | | | ±S9 | - | | |
| | TA1537 | | | ±S9 | - | | |
| Transformation assay | Syrian Golden primary HEC | plate incorporation | 12.5-200 μg/mL | NR | + | Before addition of SA7 | Greene and Friedman, 1980 |
| Transformation assay | Syrian Golden primary HEC | plate incorporation | 10.0-100.0 μg/mL | NR | + | After addition of of SA7 | Greene and Friedman, 1980 |
| Transformation assay | Syrian Golden secondary HEC | plate incorporation | 2.5-20.0 μg/mL | NR | + | Chemical transformation | Greene and Friedman, 1980 |
| Micronucleus test | NMRI mice 2 males and 2 females per dose | intraperitoneally | 2 x 122, 244 or 366 mg/kg | NA | + | + at 224 and 366 mg/kg | Wild et al., 1980 |
| Testicular DNA synthesis | C57Bl/6 x C3H mice | intraperitoneally | 100-300 mg/kg | NA | + | Significantly inhibited the incorporation of [$^{125}$I]Iododeoxy uridine into murine testicular DNA | Greene et al., 1981 |

NR = Not reported
NC = No comment
NA = Not applicable

Toluene-2,6-diamine was positive in the Salmonella typhimurium reverse mutation assay with strains TA98 and TA100, but only in the presence of S-9 (Florin et al., 1980). This compound produced negative responses in the DNA repair assay with rats (Mirsalis et al., 1982), and in the testicular DNA synthesis assay with mice (Greene et al., 1981). Positive results were obtained in the transformation assay of primary and secondary HEC both before and after the addition of SA7 (Greene and Friedman, 1980).

Toluene-3,4-diamine produced negative responses in the reverse mutation assay using four strains of Salmonella typhimurium, both with and without S-9 (Florin et al., 1980). Positive responses were obtained with this compound in the transformation assay of primary and secondary HEC (Greene and Friedman, 1980) and in the in vivo testicular DNA synthesis assay with mice (Greene et al., 1981).

## 5.3. TERATOGENICITY

In experiments with JCL:ddn mice, Inouye and Murakami (1977) found skeletal malformations in 20/109 (18%) fetuses from dams treated with a single subcutaneous injection of 50 mg/kg toluene-2,5-diamine dihydrochloride on the 8th day of pregnancy. Skeletal malformations were also observed in 7/20 (35%) fetuses from dams treated with a single subcutaneous injection of 75 mg/kg and in 17/38 (45%) fetuses from dams treated with 50 mg/kg toluene-2,5-diamine dihydrochloride intraperitoneally on the 8th day of pregnancy. Similar abnormalities were found in four fetuses from dams treated with a 50 mg/kg subcutaneous injection on days 7 and 9 of pregnancy. Statistical analyses of these data were not provided; however, no skeletal malformations were observed in the 132 fetuses examined in the control group. Other effects observed included an increased incidence of dead and resorbed fetuses and maternal deaths in dams treated with subcutaneous or

intraperitoneal doses of 75 and 50 mg/kg toluene-2,5-diamine dihydrochloride on day 8 of pregnancy (Inouye and Murakami, 1977).

Marks et al. (1981) found no teratogenic effects in CD-1 mice treated daily with intraperitoneal injections of 16, 32, 48 or 64 mg/kg toluene-2,5-diamine sulfate on days 6-15 of gestation. At doses of 64 and 48 mg/kg/day, increased incidences (4/31 and 9/11) of maternal deaths were observed compared with 0/31 for the control group. Average fetal weight decreased as the dose increased, and at dosages of 32, 48 and 64 mg/kg/day, a significant ($P<0.05$) decline in fetal weights was observed (Marks et al., 1981).

A hair-dye preparation containing 3% toluene-2,5-diamine sulfate, 4% 2,4-diaminoanisole sulfate and 2% p-phenylenediamine mixed with an equal volume of 6% hydrogen peroxide was tested for teratogenicity in 20 pregnant Charles River CD rats (Burnett et al., 1976). The formulation was applied to the skin at a dose of 2 mL/kg on days 1, 4, 7, 10, 13, 16 and 19 of gestation. Skeletal abnormalities were observed in 6/169 fetuses; this incidence was statistically significantly different from incidences in three control groups. When a group of 20 female rats was treated as above with a hair dye preparation containing 6% toluene-2,5-diamine sulfate, no significant increase in skeletal abnormalities was found in fetuses when compared with controls (Burnett et al., 1976).

## 5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding reproductive effects of the specified toluene-diamines were not located in the available literature.

## 5.5. CHRONIC TOXICITY

No overt signs of toxicity or histopathologic changes attributable to treatment were observed in Fischer 344 rats and B6C3F1 mice fed diets containing 0.06 or 0.2% (600 or 2000 ppm) and 0.06 or 1% (1000 or 600 ppm)

toluene-2,5-diamine sulfate, respectively, for 78 weeks (NCI, 1978). Experimental details were described in Section 5.1. Survival was not affected by treatment. High-dose females of both species had slightly lower body weights than did controls during the study.

No toxic effects were observed from the chronic feeding of diets containing 250 or 500 ppm, and 50 or 100 ppm toluene-2,6-diamine dihydrochloride to F344 rats and B6C3F1 mice, respectively, for 103 weeks (NCI, 1980) as described in Section 5.1. Slight, dose-related depression of mean body weights occurred in the treated female rats during the study. Survival was unaffected in both species.

In the subchronic feeding study on toluene-2,6-diamine (NCI, 1980), groups of 10 male and 10 female F344 rats of each sex were fed 0, 100, 300, 1000, 3000 or 10,000 ppm of the compound in the diet for 91 days. Body weight gain was depressed in males at all doses and in females at $\geq$1000 ppm. At 10,000 ppm, 2 of 10 males and 7 of 10 females died; no deaths occurred in any other group. At 3000 ppm, diffuse bilateral adenomatous hyperplasia of the thyroid occurred in the males, and at 10,000 ppm, nephrosis, bone marrow hyperplasia and thyroid hyperplasia occurred in both sexes. Groups of 10 male and 10 female B6C3F1 mice fed the same dietary levels of toluene-2,6-diamine as in the experiment with rats had weight gain depression at $\geq$300 ppm and renal hyperpigmentation in a few animals at 1000 ppm (NCI, 1980). No deaths occurred at any dose level and no other effects were noted.

No signs of toxicity were observed in 50 male and 50 female Swiss Webster mice treated dermally once a week or once every other week for 18 months with 0.05 mℓ of a hair-dye formulation containing 1 volume of 3% toluene-2,5-diamine sulfate mixed with an equal volume of 6% hydrogen peroxide (Burnett et al., 1975).

Doses of 0.5 mℓ of hair-dye formulations containing 1 volume of 4 or 3% toluene-2,5-diamine sulfate mixed with an equal volume of 6% hydrogen peroxide were applied to the skin of 50 male and 50 female Sprague-Dawley rats twice weekly for 2 years (Kinkel and Holzmann, 1973). No differences were observed in behavior, feeding, body-weight gain, hematological parameters, mean lifespan, mortality or liver function (serum transaminase and bromosulfthalein secretion). No pathologic changes were observed at necrospy (Kinkel and Holzmann, 1973).

## 5.5. OTHER RELEVANT INFORMATION

The following $LD_{Lo}$s have been reported for toluene-2,5-diamine (NIOSH, 1978):

oral - unspecified mammal: 3600 mg/kg
subcutaneous - rat: 50 mg/kg
- rabbit: 100 mg/kg

The oral $LD_{50}$ of toluene-2,5-diamine sulfate in an oil-in-water emulsion in rats was reported as 98 mg/kg; the intraperitoneal $LD_{50}$ of the compound in dimethylsulfoxide in rats was 49 mg/kg (Burnett et al., 1977).

Female Sprague-Dawley rats receiving 33.3 or 50 mg/100 g body weight toluene-3,4-diamine by gavage twice daily for 5 days developed duodenal ulcers (Selye, 1973; Selye and Mecs, 1974). Single subcutaneous injections of 62.5-500 mg/kg toluene-3,4-diamine to male and female Sprague-Dawley rats resulted in gastric and duodenal lesions (Perkins and Greene, 1975).

## 6. AQUATIC TOXICITY

### 6.1. ACUTE TOXICITY

The effects of toluene-2,3-diamine were determined on guppies, Poecilia reticulata, and the water flea, Daphnia magna (Crustacea) (Smirnova et al., 1967). Data available in the abstract of this Russian study indicate that exposure to 200 mg toluene-2,3-diamine/ℓ (time unspecified) caused no observable effects on P. reticulata. Daphnia were more sensitive, with a toxicity threshold at 2 and 5 mg/ℓ causing death after 510 days of exposure.

### 6.2. CHRONIC EFFECTS

Pertinent data regarding the effects of chronic toluenediamine exposure were not located in the available literature.

### 6.3. PLANT EFFECTS

An abstract from a Russian study (Smirnova et al., 1967) indicated that no toxic effects were evident in the green alga, Scenedesmus obliquus, after exposure to toluene-2,3-diamine. Toxicant concentration and exposure duration, however, were not specified.

### 6.4. RESIDUE

Veith et al. (1979) reported that the BCF for toluenediamine was 91 (log BCF = 1.96) in fathead minnows, Pimephales promelas, exposed at 0.001 mg/ℓ for 32 days.

### 6.5. OTHER RELEVANT INFORMATION

Additional data relevant to the toxicity of toluenediamine to aquatic organisms were not located in the available literature.

## 7. EXISTING GUIDELINES AND STANDARDS

### 7.1. HUMAN

Pertinent data regarding existing guidelines and standards for the toluenediamines were not located in the available literature.

### 7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of toluenediamine were not located in the available literature.

## 8. RISK ASSESSMENT

Toluene-2,5-diamine sulfate was tested for carcinogenicity by the NCI (1978), Kinkel and Holzmann (1973), Burnett et al. (1975) and Giles et al. (1976). No carcinogenic effects were seen in rats administered 0, 0.06 or 0.2% and in mice administered 0, 0.06 or 0.10% toluene-2,5-diamine sulfate in the diets for 78 weeks (NCI, 1978). No carcinogenic effects were seen in mice or rats receiving dermal applications of toluene-2,5-diamine sulfate in hair-dye preparations (Burnett et al., 1975; Giles et al., 1976; Kinkel and Holzman, 1973). Sufficient evidence was not obtained to demonstrate the carcinogenicity of toluene-2,6-diamine dihydrochloride in rats fed 50, 250 or 500 ppm or in mice fed 50 or 100 ppm of the compound in the diet for 103 weeks (NCI, 1980).

Toluene-2,5-diamine produced positive results in a reverse mutation assay with S. typhimurium TA1538 (Ames et al., 1975) and in the transformation assay with hamster embryo cells (Greene and Friedman, 1980), negative results in the in vivo micronucleus assay with rats, and positive results in the in vivo testicular DNA synthesis assay with mice (Greene et al., 1981).

Toluene-2,6-diamine gave positive results were obtained with toluene-2,5-diamine in a reverse mutation assay with two strains (TA98 and TA100) of S. typhimurium (Florin et al., 1980) and in the transformation assay with hamster embryo cells (Greene and Friedman, 1980). Negative results were obtained in the in vivo DNA repair assay (Mirsalis et al., 1982) and the testicular DNA synthesis assay (Greene et al., 1981).

Toluene-2,5-diamine sulfate and toluene-2,6-diamine dihydrochloride failed to demonstrate oncogenic activity in rats or mice fed these compounds in the diet; however, positive results were obtained from both of these compounds in in vitro mutagenicity assays with bacteria and hamster embryo

cells. Although these compounds exhibited positive mutagenic activity in two test systems, the lack of conclusive evidence for the tumorigenicity of toluene-2,5-diamine sulfate and toluene-2,6-diamine dihydrochloride preclude the classification of these compounds as carcinogens.

Toluene-3,4-diamine produced negative results in the reverse mutation assay with four strains of S. typhimurium bacteria (Florin et al., 1980) and positive results in the transformation assay with hamster embryo cells (Greene and Friedman, 1980) and the in vivo testicular DNA synthesis assay (Greene et al., 1981).

At dose levels of 50 and 75 mg/kg administered subcutaneously and 50 mg/kg administered intraperitoneally to mice on day 8 of gestation, toluene-2,5-diamine dihydrochloride induced skeletal malformations in fetuses (Inouye and Murakami, 1977). At dose levels of 16, 32, 48 or 64 mg/kg of toluene-2,5-diamine sulfate administered intraperitoneally to mice on days 6-15 of gestation, no teratogenic effects were observed. Maternal toxicity was observed at the 64 and 48 mg/kg doses; fetal weight decreased at doses of 32, 48 and 64 mg/kg/day (Marks et al., 1981). Skeletal abnormalities were observed in the offspring of pregnant rats dermally treated with hair-dye preparations containing a 1:1 mixture of 3% toluene-2,5-diamine sulfate and 6% hydrogen peroxide on days 1, 4, 7, 10, 13, 16 and 19 of gestation (Burnett et al., 1976). No significant increases in skeletal abnormalities were observed in fetuses whose mothers had been treated in a similar manner with a hair-dye preparation containing 6% toluene-2,5-diamine sulfate (Burnett et al., 1976).

There is little information regarding the effects of chronic exposure to toluenediamine or the four specified isomers. The chronic dietary studies of the NCI (1978, 1980) appear to identify NOAELs in rats of 2000 ppm for

toluene-2,5-diamine sulfate and 500 ppm for toluene 2,6-diamine hydrochloride, as weight gain depression was observed in females at these dose levels, but no overt signs of toxicity or histopathologic changes attributable to treatment were found.

Using the NOAEL of 500 ppm toluene-2,6-diamine dihydrochloride in rats, derived from the NCI (1980) study, an ADI value can be derived. In lieu of food consumption data, the assumption must be made that a rat consumes a daily amount of food equivalent to 5% of its body weight. Using this assumption, an equivalent dose of 25.0 mg/kg/day can be calculated. Since these data are for the dihydrochloride salt of toluene-2,6-diamine (MW=195.10), an equivalent dose of 15.7 mg/kg/day for toluene-2,6-diamine (MW=122.2) must be used to calculate an ADI. An ADI value of 11.0 mg/day for a 70 kg human can be calculated by multiplying the animal dose by an assumed human body weight of 70 kg and applying an uncertainty factor of 100, to convert from experimental animal data to human data, and to protect the more sensitive individuals of a population.

The subchronic feeding study by the NCI (1980) provides additional data that can contribute to the identification of a threshold for toxicity of this chemical to rats. This study appears to define a NOAEL in rats for toluene-2,6-diamine at 1000 ppm. Although body weight gain was depressed, no significant adverse effects were observed at this dietary level. Thyroid hyperplasia was observed at 3000 ppm and frank toxic effects, including high mortality, occurred at 10,000 ppm. The NOAEL of 1000 ppm supports the NOAEL of 500 ppm previously identified in the chronic study (NCI, 1980). The NOAEL of 500 ppm was deemed more appropriate for derivation of an ADI because of the greater number of animals and extended exposure in the chronic study.

The ADI values for toluene-2,5-diamine sulfate can be calculated in the same manner, using the NOAEL of 2000 ppm identified in the dietary study in rats (NCI, 1978). Assuming that a rat consumes a daily amount of food equivalent to 5% of its body weight, an equivalent dose of 100 mg/kg/day can be calculated. The corresponding dose for toluene-2,5-diamine (the data are for the sulfate salt of the compound, molecular weight of 220) is 55.5 mg/kg/day. An ADI value of 38.9 mg/day can be calculated by multiplying the animal dose by an assumed human body weight of 70 kg and applying an uncertainty factor of 100.

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## APPENDIX: LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

These searches were conducted in May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:


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